Amendments to the Drawings

The attached sheets of drawings include new sheets of drawings for Figures 4-9 and 12-17. The drawings have been submitted to improve the clarity of symbols used in the Figures 4-9, 13-15, and 16. In view of the changes made to these figures, which were originally filed on sheets with two drawings per sheet, New Sheets are enclosed for each of Figures 4-9 and 12-17. These sheets, which include Figures 4, 5, 6, 7, 8, 9, 12, 13, 14, 15, 16, and 17 are New Sheets that replace the original sheets of these Figures.

Attachment: Twelve New Sheets

REMARKS

Applicants thank Examiner Minnifield for her time and comments during a telephone conference with the undersigned representative on December 5, 2005. Objections to the Drawings were discussed. Upon review of the drawings during the teleconference, the undersigned representative and Examiner Minnifield agreed that additional drawings (*e.g.*, Figures 6, 8, 9, 12, 15, and 16) and not only Figure 4, which was objected to for lack of formality in the Office Action dated November 9, 2005, would be replaced with formal drawings. In addition, Applicants' representative noted that the Office Action (paragraph 3, page 2) stated that a Notice to Comply with Requirements for Patent Applications Containing Nucleotide Sequence and/or Amino acid Sequence Disclosures was attached; however, the document was not present in the mailing from the U.S. Patent and Trademark Office as stated in the Action. During the teleconference, Examiner Minnifield indicated that the asserted lack of compliance with sequence disclosure requirements related to the lack of sequence identifying numbers cited in the specification for sequences described in the specification.

Reconsideration of the present application is respectfully requested in view of the Amendment submitted herewith and the following remarks. Claims 1-18 were pending in the Application. Claims 1, 2, 11, and 12 have been hereby canceled. Claims 3-10 and 13-18 have been amended and new claim 19 has been added to point out with more particularity and to claim distinctly certain embodiments of Applicants' invention. Claims 3-10 and 13-19 are therefore currently under examination. The above Amendment is not to be construed as acquiescence to the stated grounds for objection or rejection and is made without prejudice to prosecution of any subject matter modified or removed by this amendment in a related divisional, continuation, or continuation-in-part application. No new matter has been added to the application. Support for the amended claims may be found throughout the specification, for example, at page 15, line 15; page 18, line 22 through page 19, line 11; page 19, line 27 through page 20, line 2; and page 21, lines 7-19.

The enclosed electronic and paper copies of the Sequence Listing include no new matter that goes beyond the original application as filed, but are supplied to fulfill the requirements as outlined in the Office Action. Furthermore, the above amendments, which merely direct the

insertion of sequence identifiers and the Sequence Listing include no matter that goes beyond the original application as filed. Applicants respectfully submit that the above-identified application is now in compliance with 37 C.F.R. §§ 1.821-1.825.

Objection to the Drawings

In the Office Action dated November 9, 2005, the Examiner has objected to Figure 4 of the disclosure, asserting that the symbols in the illustrated graph cannot be distinguished.

Applicants have submitted herewith a replacement drawing for Figure 4. In addition, Applicants also have submitted replacement drawings for Figures 4-9, 13-15, and 16 to improve the clarity of symbols used in the figures. In view of the changes made to Figures 4-9, 13-15, and 16, which were originally filed on sheets with two drawings per sheet, New Sheets are enclosed for Figures 4-9 and 12-17. No new matter has been added to the drawings. Applicants respectfully submit that all drawings meet the requirements under 37 C.F.R. §§ 1.84 and 1.121 and request that this objection be withdrawn.

Requirement to Comply with 37 C.F.R. §§ 1.821-1.825

The Examiner has requested compliance with the requirements of 37 C.F.R. §§ 1.821-1.825 with respect to the sequence disclosures for reasons set forth in a Notice to Comply with Requirements for Patent Applications Containing Nucleotide And/Or Amino Acid Sequence Disclosures. Although the Action indicated that the Notice was attached to the Action, Applicants note that the Notice did not accompany the Office Action.

In accordance with 37 C.F.R. §§ 1.821-1.825, Applicants have amended the Sequence Listing to include sequence-identifying numbers (SEQ ID NO.) for peptide sequences disclosed in the specification as originally filed. In addition, the specification has been hereby amended to insert sequence-identifying numbers adjacent to these sequences described in the specification. Applicants respectfully submit that no new matter has been added to the application. Applicants note that in a Preliminary Amendment submitted to the U.S. Patent and Trademark Office on August 19, 2004, the specification was amended to include sequence-identifying numbers for paragraphs on page 4 (second paragraph); page 15 (first, second, and paragraph bridging page 15

and 16); page 16 (first paragraph); and page 21 (second paragraph). Applicants respectfully submit that the present application complies with the sequence disclosure requirements under 37 C.F.R. §§ 1.821-1.825 and therefore request that this objection be withdrawn.

Objections to Claims for Informalities

The Examiner has objected to claims 6 and 16-18 for lack of formality. The Examiner asserts that claim 6 recites "peptideantigen," which should be --peptide antigen--. The Examiner asserts that claims 16-18 recite "of treatment *of* prophylaxis," which properly should read --of treatment *or* prophylaxis--.

In the copy of the Application as filed, claim 6 recites peptide and antigen as two distinct words. In the published application, however, due to a transcriptional error by the PTO during publication, the space between the two words was inadvertently deleted. In the Listing of Claims provided herein, the correct recitation of "peptide antigen" is shown in claim 6.

Applicants thank the Examiner for pointing out the inadvertent typographical error in claim 16. According to the Amendment submitted herewith, claim 16, upon which claims 17 and 18 depend, has been amended to recite --treatment or prophylaxis--.

Applicants respectfully submit that the present claims meet the formality requirements and request that these objections to claims 6 and 16-18 be withdrawn.

Rejections Under 35 U.S.C § 112, First Paragraph (Enablement)

The Examiner has rejected claims 1-5 and 7-18 under 35 U.S.C. § 112, first paragraph, for allegedly lacking enablement. The Examiner asserts that the scope of the claims is not commensurate with the subject matter enabled by the disclosure. The Examiner concedes that the specification enables a person skilled in the art to make and use a vaccine composition comprising a peptide having the sequence set forth in SEQ ID NO:2 and a proteosome, and a vaccine composition comprising MtsA and a proteosome; however, the Examiner asserts that the specification does not enable a person skilled in the art to make and use a vaccine composition comprising a streptococcal protein H peptide.

Applicants respectfully traverse this rejection and submit that as disclosed in the specification and recited in the instant claims, Applicants fully enabled the presently claimed

subject matter at the time the application was filed. Applicants submit that in view of the Amendment submitted herewith, which includes cancellation of claims 1, 2, 11, and 12 without acquiescence or prejudice, rejection of these claims has been rendered moot.

As provided in the teachings of the application, the specification enables a person skilled in the art to make and use, readily and without undue experimentation, vaccine compositions comprising a proteosome adjuvant and at least one group A Streptococcal antigen attached to a hydrophobic moiety, wherein the antigen comprises an antigenic peptide between 6 and 25 amino acids in length from the conserved C-terminal region of a group A streptococcal M protein (*see, e.g.,* page 15, lines 1-27). The specification describes that group A streptococcal M proteins have a conserved region in the carboxy terminus that may be useful for inducing an immune response to more than one serotype of *S. pyogenes* without inducing antibodies that may cross-react with human proteins (*see, e.g.,* page 15, lines 1-27; Figure 1). The specification further provides an example of such a peptide (SEQ ID NO:1) in this conserved carboxy terminal region (*see, e.g.,* page 15, lines 1-15).

The conserved carboxy terminal antigenic peptide of SEQ ID NO:1 may further comprise flanking amino acids that maintain the helical conformation of the antigenic peptide in the vaccine composition (*see, e.g.,* page 15, lines 16-23). An exemplary amino acid sequence of such a peptide is provided in SEQ ID NO:2. Thus, as described in the application and as acknowledged by the Examiner, the specification enables a person skilled in the art to make and use a vaccine composition comprising the antigenic peptide, SEQ ID NO:2, and a proteosome adjuvant (*see also, e.g.,* Examples, at pages 29-40).

The specification also teaches a person skilled in the art to make and use, readily and without undue experimentation, a vaccine composition comprising a proteosome adjuvant and a group A streptococcal antigen, wherein the antigen is selected from an MtsA peptide or a protein H peptide. As acknowledged by the Examiner, the specification teaches a person skilled in the art how to make and use a vaccine composition comprising a proteosome and an MtsA antigen from *S. pyogenes*. Exemplary Mts peptides are described in the specification, and a working example demonstrates the immune response elicited in animals that were immunized with an MtsA peptide (*see, e.g.,* page 15, line 28 through page 16, line 13; page 38, Table 13).

In addition, and contrary to the assertion by the Examiner, the instant application also enables a person skilled in the art to make and use a protein H peptide. Protein H from *S. pyogenes* is an M-like protein that is derived from the strain AP1 (*see, e.g.,* page 16, lines 8-13). Exemplary peptides of protein H include APP and KQL30 (SEQ ID NO:4) (*see, e.g.,* page 3, lines 28-32; page 16, lines 8-13 and references cited therein). Furthermore, the instant application describes in a working example that a protein H peptide induced an immune response in animals, which resulted in an increased percent of animals surviving challenge with *S. pyogenes* (*see, e.g.,* page 38, line 1 through page 39, line 3). The immunized animals also produced antibodies that had opsonic activity (*see, e.g.,* page 38, Table 13). Thus, given the extensive teachings in the present application regarding vaccine compositions comprising a proteosome adjuvant and a group A streptococcal antigen, a person skilled in the art is enabled to make and use, readily and without undue experimentation, a vaccine composition comprising a proteosome adjuvant and a group A streptococcal antigen that is a protein H peptide.

Applicants disagree with the assertion by the Examiner that the state of the art supports the Examiner's allegation that the present application does not enable a person skilled in the art to make and use the claimed compositions and methods. The documents cited by the Examiner (Hayman et al., *Immunol. Cell Biol.* 80:178-87 (2002); Olive et al., *Vaccine* 20:2816-25 (2002)) instead show that a need exists for a vaccine composition that is capable of inducing an immune response in an individual for treatment and/or prophylaxis of group A streptococcal infections. The present application describes and claims vaccine compositions and related methods that provide a solution to the problem recognized in the art. Furthermore, as discussed herein, the specification teaches persons skilled in the art how to make and use these claimed vaccine compositions.

Accordingly, given the disclosure of the present application, which includes several working examples, the specification enables a skilled artisan to make and use the claimed vaccine compositions and methods, readily and without undue experimentation. Applicants therefore respectfully submit that the application satisfies all requirements under 35 U.S.C. § 112, first paragraph, and request that this rejection be withdrawn.

Rejection Under 35 U.S.C. § 102

The Examiner has rejected claims 1-3, 8, 9, 11, 14, and 16 under 35 U.S.C. § 102(b) for allegedly being anticipated by Lowell et al. (*in Technological Advances in Vaccine Development*, pp. 423-432 (1988)). Applicants submit that in view of the Amendment submitted herewith, which includes cancellation of claims 1, 2, and 11, without acquiescence or prejudice, rejection of these claims has been rendered moot.

Applicants respectfully traverse this rejection and submit that Lowell et al. fail to teach or suggest each feature of the pending claims; therefore, the document does not destroy the novelty of the presently claimed invention. Lowell et al. do not teach or suggest a vaccine composition that comprises a proteosome adjuvant and at least one group A Streptococcal antigen, wherein the antigen comprises an antigenic peptide between 6 and 25 amino acids in length from the conserved C-terminal region of a group A streptococcal M protein. Lowell et al. also do not teach or suggest that the antigenic peptide may further comprise flanking amino acid sequences that maintain the helical folding of the antigen; nor do Lowell et al. teach or suggest a spacer peptide comprising at least two glycine residues, wherein the spacer peptide links the antigenic peptide with the hydrophobic moiety. Lowell et al. instead describe peptides from the amino terminal portions of M6 and M24 proteins that are specific to those respective serotypes (*see* Lowell et al., page 425 and references cited therein).

Accordingly, the cited document fails to anticipate the features of the present claims. Applicants respectfully submit that the currently pending claims meet the requirements for novelty under 35 U.S.C. § 102 and request that the rejection of these claims be withdrawn.

Rejections Under 35 U.S.C. § 103

The Examiner has rejected claims 4-6 under 35 U.S.C. § 103(a) for allegedly being obvious over Lowell et al. (*in Technological Advances in Vaccine Development*, pp. 423-432 (1988)) as applied to claims 1-3, 8, 9, 11, 14, and 16 as set forth in the rejection for lack of novelty, and in further view of Brandt et al. (*Nat. Med.* 6:455-59 (2000)). The Examiner has also rejected claims 10-18 under 35 U.S.C. § 103(a) for allegedly being obvious over Lowell et al. and Brandt et al. as applied to claims 1-6, 8, 9, 11, 14, and 16, and in further view of Relf et al. (*Adv. Exp. Med. Biol.* 418:859-61 (1997)). The Examiner asserts that combining the teachings of

Lowell et al., that adjuvants other than alum are needed for human use, and the teachings of Brandt et al., that describe a group A streptococcal antigen having the amino acid sequences set forth in SEQ ID NO:1 and 2, would be obvious to a person having ordinary skill in the art. With respect to claims 10-18, the Examiner asserts that Relf et al. teach intranasal administration of a group A streptococcal vaccine and that by combining the teachings of Relf et al. with Lowell et al. and Brandt et al., a person having ordinary skill in the art would obtain the presently claimed embodiments of Applicants' invention.

Applicants respectfully traverse these rejections and submit that the present claims as amended herewith meet the statutory requirements for nonobviousness under 35 U.S.C. § 103. Applicants submit that the PTO has not established a *prima facie* case of obviousness. *See In re Mayne*, 104 F.3d 1339, 1341-43, 41 U.S.P.Q.2d 1451 (Fed. Cir. 1997) (The PTO has the burden of showing a *prima facie* case of obviousness.). The PTO must show (1) that the references teach or suggest all claim limitations; (2) that the references provide some teaching, suggestion, or motivation to combine or modify the teachings of the prior art to produce the claimed invention; and (3) that the combined teachings of the references indicate that by combining the references, a person having ordinary skill in the art will achieve the claimed invention with a reasonable expectation of success. When rejection of claims depends upon a combination of prior art references, something in the prior art as a whole must suggest the desirability, thus the obviousness, of making the combination (*see In re Rouffet*, 149 F.3d 1350, 1355, 47 U.S.P.Q.2d 1453 (Fed. Cir. 1998)).

The cited documents, either alone or in any combination, fail to teach or suggest a vaccine composition comprising a proteosome adjuvant and at least one group A streptococcal antigen attached to a hydrophobic moiety, wherein the antigen comprises an antigenic peptide between 6 and 25 amino acids in length located in the conserved C-terminal region of a group A streptococcal M protein. As acknowledged by the Examiner, Lowell et al. do not teach or suggest a vaccine composition that comprises a proteosome adjuvant and at least one group A Streptococcal antigen comprising an antigenic peptide between 6 and 25 amino acids in length from the conserved C-terminal region of a group A streptococcal M protein. Lowell et al. instead describe peptides from the amino terminal portions of M6 and M24 proteins that are

specific to the respective M6 and M24 serotypes (*see* Lowell et al., page 425 and references cited therein). Brandt et al. fail to teach or suggest a vaccine composition comprising a proteosome adjuvant and further fail to teach or suggest that the group A streptococcal antigens described therein may be attached to a hydrophobic moiety and combined with a proteosome adjuvant. By contrast, Brandt et al. teach that a suitable vaccine candidate might consist of at least two streptococcal antigens: a conserved M protein determinant in combination with N-terminal serotypic peptides of a group A streptococcal M protein (*see, e.g.,* Abstract therein). Even assuming *arguendo* that the cited documents disclosed each feature of the pending claims, absent some teaching or suggestion to combine features of a claimed invention that are present in the cited art, establishing obviousness on the basis that separate features existed in the prior art is insufficient (*see Ruiz and Foundation Anchoring Systems, Inc. v. A.B. Chance Company*, 234 F.3d 654, 665 (Fed. Cir. 2000)).

None of the cited documents provides any motivation, teaching, or suggestion that by combining or modifying individual teachings of each document a person having ordinary skill in the art would reasonably expect to achieve Applicants' claimed compositions and methods. Lowell et al. do not teach or suggest any desirability to combine a proteosome adjuvant with any other streptococcal antigen, and neither Brandt et al. nor Relf et al. teach or suggest or indicate any desirability to combine an antigenic peptide from the conserved C-terminal region of a group A streptococcal M protein with a proteosome adjuvant. Brandt et al. describe challenges in development of a group A streptococcal vaccine and suggest that "it would seem wise to not rely solely on the J14 epitope alone in a vaccine" (*see* page 458, column 1), thereby teaching away from the presently claimed compositions and methods. Relf et al. teach that a systemic and mucosal immune response in animals immunized with conserved protein M fragments and serotype specific M protein fragments varied with the adjuvant and carrier polypeptide used in a vaccine composition (*see, e.g.,* page 860). While the cited documents suggest a need or desire to obtain a group A streptococcal vaccine, nowhere do the publications teach or suggest Applicants' solution to the problem. Only with impermissible hindsight using the teachings in the present application, can the Examiner assert that an ordinarily skilled person would expect to achieve successfully a vaccine composition comprising a proteosome adjuvant and at least one group A

Streptococcal antigen attached to a hydrophobic moiety, wherein the antigen comprises an antigenic peptide between 6 and 25 amino acids in length from the conserved C-terminal region of a group A streptococcal M protein, which, in certain embodiments, is formulated for mucosal administration, including, for example, intranasal administration.

Applicants therefore respectfully submit that a *prima facie* case of obviousness has not been established and that the claimed subject matter is nonobvious as required under 35 U.S.C. § 103. Applicants respectfully request that these rejections of the claims be withdrawn.

Applicants submit that pending claims 3-10 and 13-19 in the application are allowable. Favorable consideration and a Notice of Allowance are earnestly solicited.

Respectfully submitted,

SEED Intellectual Property Law Group PLLC

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MJR:teb

Enclosures:
12 Sheets of Drawings (Figures 4-9 and 12-17)

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